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Gene Therapy And Accelerated Approval: US FDA Mulls Pooling Data To Shrink Postmarket Studies

by Sarah Karlin-Smith

The head of CBER's Office of Therapeutic Products also touted hiring achievements and new communication plans with sponsors at an Alliance for Regenerative Medicine meeting.

The US Food and Drug Administration is considering how to reduce the sample sizes needed for postmarket studies of cell and gene therapy, a move that could ease some of the burden of long-term follow up for the one-time treatments.

Cell and gene therapy sponsors who receive accelerated approval may be able to lower the number of patients needed in postmarket trials by leveraging data from the therapy's use in other indications, Nicole Verdun, director of the Center for Biologics Evaluation and Research's Office of Therapeutic Products, said during an Alliance For Regenerative Medicine (ARM) event 15 July.

'Ripe For Public Discussion'

Due to the newness of the space and the slow progression of some of the diseases being treated, the FDA wants sponsors to track gene therapy recipients for up to 15 years, which includes substantial challenges.

Key Takeaways

- The Office of Therapeutic Products is considering ways to optimize postmarket studies and may hold a public meeting to encourage sponsors to collaborate.
- The OTP director suggested the office's thinking about sponsor communication has shifted in recent years and encourages companies to seek advice before investing time and money "doing the wrong thing."
- The new super office in CBER is nearly

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Verdun said long-term follow up is something she would "like to get a little bit more handle on," particularly in the rare disease space, where the agency is approving more products using "accelerated approval-type endpoints."

fully staffed, but wants resources to hire more reviewers and improve its infrastructure.

One difficulty is that patients who had a significant disease burden before receiving the gene therapy, but then are able to live a very different life after treatment often feel they do not need follow-up care or don't want to spend their time on it, Verdun said.

Other challenges include investigators changing jobs or gene therapy programs that close after they have dosed patients.

"There are ways we can leverage larger organizations or repositories or government agencies," Verdun said. "All of that has been explored without an answer. And really, who holds the data, the obligation, the responsibility after a program folds even? What do we do to try and maintain this sort of data."

The topic is "really ripe for public discussion or conversation," Verdun said, perhaps a signal the agency wants outside input. In October 2023 she told the *Pink Sheet* that the FDA may need a public meeting on the subject. (Also see "*US FDA Struggling With Long-Term Follow-Up Requirements For Gene Therapies*" - Pink Sheet, 18 Oct, 2023.)

In May 2023, industry urged the FDA to consider standardizing gene therapy postmarket methods and trials. (Also see "*Long-Term Postmarket Studies For Gene Therapies May Need To Be Combined, Standardized*" - Pink Sheet, 7 May, 2023.)

CBER has gone all in on the use of accelerated approval in gene therapy (Also see "*Accelerated Approval Now Starting Point For Gene Therapy Development, US FDA's Marks Says*" - Pink Sheet, 28 Feb, 2024.), despite concerns about the ability to gather crucial long-term safety and efficacy data, and the risk patients may not be eligible for newer gene therapies after receiving a product. (Also see "*Gene Therapy: Years After Accelerated Approval, Will US FDA Still Be Asking 'Does It Work?'*" - Pink Sheet, 20 Feb, 2023.) and (Also see "*US FDA's Marks Willing To Accept Gene Therapies Occasionally Not Confirming Benefit*" - Pink Sheet, 5 Dec, 2023.)

Verdun previously indicated her willingness to be flexible in other ways for cell and gene therapy, including acknowledging that sometimes it will be impracticable for accelerated approval confirmatory trials to be underway at the time of approval. (Also see "*FDA Gene Therapy Office Chief Prefers Flexibility With Accelerated Approval Confirmatory Trials*" - Pink Sheet, 23 Sep, 2023.) She also recently said the FDA is applying platform designation principles to situations

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that may not technically qualify for the program to speed cell and gene therapy approvals in multiple indications. (Also see "*US FDA Using Platform Ideas Outside Of Formal Designations To Speed Cell and Gene Approvals*" - Pink Sheet, 14 May, 2024.)

START Comms For All

Her inclusive approach also is expanding to communications.

Verdun said during the meeting that she is "leaning into the principles" of the agency's new START pilot program and and trying to apply many of its perks to applications that have not been formally accepted.

START, or the "Support for clinical Trials Advancing Rare disease Treatment" pilot, was designed to provide enhanced FDA-sponsor communication akin to the process developed for the Operation Warp Speed COVID-19 vaccine development program. (Also see "*Three Gene Therapies, Moderna Metabolic Drug In Inaugural START Class; CBER Oversubscribes*" - Pink Sheet, 6 Jun, 2024.)

Verdun told applicants to not be afraid of seeking FDA advice. (Also see "*US FDA's Cell-Gene Therapy Office Head Wants Sponsors To Seek Out Meetings*" - Pink Sheet, 12 Jun, 2024.)

"Come back and talk to us if something isn't working," she said, referencing a recent meeting where someone came to her after not being able to enroll patients for two years.

Verdun discussed the issue with the person "and fixed a quick thing and they were very appreciative."

"But we have to be able to have that dialogue, things evolve, the field evolves," she said.

An audience member pushed Verdun on the enhanced communication program, saying that "historically when sponsors have come to the agency, we get the clear message: We're not your consultant. So you want us to bring a fully-fleshed out proposal based on data," which means companies often incur a lot of sunk costs before learning the FDA does not like the proposal, the audience member explained.

"Are we seeing a transition to where there's going to be greater opportunity to discuss things in more of a theoretical way, to discuss how can we get there?" the person asked. "What are the concepts that get us from here to there without [having] to put a lot of effort into the data generation that may or may not be helpful in the long run?"

"We do have some early phase types of meetings where we can have those types of conversations," Verdun said. "And to your point, we can't be regulatory consultants, but we can

give advice based on a plan. So those are to me two different things. We can't say you need to do a through z and we're going to write it out for you. But if you have a plan of what the assay is going to look like or what it's going to involve, we should be able to answer those questions about whether you're on the right path or not. A lot of people use INTERACT meetings to do that, to have those conversations at least recently and just early phase meetings." (Also see "*INTERACT Meeting Timing Remains Point Of Confusion*" - Pink Sheet, 1 Jul, 2024.)

Verdun acknowledged the agency's practices may have been different in the past, but said staff are having those conversations now and that she encourages them.

"It doesn't make sense to invest a whole lot of time and money and then for us to say that's the wrong thing," Verdun said.

Most OTP Positions Filled, But Could Use More Staff

Verdun told ARM that her relatively new super office has filled "most" of the positions for which it has been given resources.

"So very few are remaining, so we really are sort of at capacity," she said, adding that OTP's capacity needs to grow.

OTP's predecessor office, the Office of Tissues and Advanced Therapies (OTAT) received funding for 125 new positions in the last prescription drug user fee cycle. In February, the FDA said the office was at about 75%-80% of its full staffing allotment. (Also see "*US FDA Gene Therapy Staff-Up: Glass Three-Quarters Full?*" - Pink Sheet, 29 Feb, 2024.)

The agency did not respond to a question about the number of positions that have been filled, remain empty or are needed in addition to existing resources.

Verdun said the FDA needs more reviewers and resources to enhance its infrastructure as work scales up.